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Myocardial Sympathetic Innervation and Long-Term Left Ventricular Mechanical Unloading

Stavros G. Drakos, MD,* Theodoros Athanasoulis, MD,† Konstantinos G. Malliaras, MD,* John V. Terrovitis, MD,* Nikolaos Diakos, MD,* Dimitrios Koudoumas, MD,* Argirios S. Ntalianis, MD,* Stergios P. Theodoropoulos, MD,‡ Magdi H. Yacoub, MD,‡§ John N. Nanas, MD, PHD*

Athens, Greece; and Harefield, United Kingdom

OBJECTIVES The purpose of this study was to analyze the effects of left ventricular assist devices (LVADs) on myocardial sympathetic innervation of the failing heart.

BACKGROUND Ventricular unloading by LVADs seems to cause reverse remodeling of the failing heart, but little is known about the sympathetic nerve activity during long-term mechanical unloading.

METHODS We studied the effects of LVADs on myocardial sympathetic innervation, by iodine 123-*meta*-iodobenzylguanidine (^{123}I-*m*IBG) scintigraphy performed before and 3 months after LVAD implantation in 12 end-stage heart failure patients. We calculated the: 1) heart-to-mediastinum (H/M) uptake ratio on early and delayed images, indicating myocardial accumulation of ^{123}I-*m*IBG; and 2) rate of ^{123}I-*m*IBG washout after initial accumulation. Similar ^{123}I-*m*IBG imaging and functional and hemodynamic measurements were made 3 months apart in 6 other heart failure patients not treated with an LVAD.

RESULTS After 3 months of LVAD support, the mean left ventricular ejection fraction had increased from 19 ± 6% to 29 ± 9% ($p = 0.006$), peak oxygen consumption increased from 9 ± 4 ml/kg/min to 13 ± 3 ml/kg/min ($p = 0.058$), serum sodium increased from 135 ± 4 mEq/l to 140 ± 2 mEq/l ($p = 0.014$), whereas the left ventricular end-diastolic diameter decreased from 72 ± 7 mm to 56 ± 3 mm ($p = 0.002$), pulmonary capillary wedge pressure decreased from 30 ± 6 mm Hg to 5 ± 3 mm Hg ($p = 0.012$), serum creatinine decreased from 1.5 ± 0.6 mg/dl to 1.0 ± 0.4 mg/dl ($p = 0.011$), and B-type natriuretic peptide decreased from 2,279 ± 1,900 pg/ml to 102 ± 5 pg/ml ($p = 0.003$). After 3 months of LVAD, the H/M ratio increased on delayed images from 1.25 ± 0.18 to 1.43 ± 0.13 ($p = 0.01$) and on early images from 1.35 ± 0.19 to 1.44 ± 0.11 ($p = 0.028$), and the washout rate decreased from 51.0 ± 23.2% to 30.6 ± 8.7%, ($p = 0.015$). There was a significant correlation between the late H/M *m*IBG ratio and B-type natriuretic peptide ($R = 0.77$, $p = 0.01$) and systolic pulmonary pressure ($R = 0.7$, $p = 0.05$). No significant scintigraphic, functional or hemodynamic change was observed between the 2 evaluations in the 6 patients not treated with an LVAD.

CONCLUSIONS Ventricular unloading caused clinical, functional, and hemodynamic improvements accompanied by improvements in sympathetic innervation in the failing heart. (J Am Coll Cardiol Img 2010;3:64–70) © 2010 by the American College of Cardiology Foundation

From the *3rd Cardiology Department and Department of Clinical Therapeutics, University of Athens, Athens, Greece; †Division of Nuclear Medicine, Alexandra Hospital, Athens, Greece, ‡Division of Cardiothoracic Surgery, IASO General Hospital, Athens, Greece; and the §Harefield Heart Science Center and the Magdi Yacoub Institute, Harefield, United Kingdom. Dr. Drakos is currently working at the Division of Cardiology and the Molecular Medicine Program, University of Utah, Salt Lake City, Utah.

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Mechanical circulatory support with left ventricular assist devices (LVADs) has become a standard bridge to cardiac transplantation (1) and has also been approved as destination therapy for selected patients presenting with end-stage heart failure (HF) (2). Clinical applications of LVAD have shown that it might reverse the complex process of chronic left ventricular (LV) remodeling to a degree where a subset of patients can be weaned from the device after the return of essential cardiac function (3–6). Specifically, LVAD profoundly unloads LV volumes and pressures, reversing the compensatory and stress responses of the overloaded myocardium and causing its structural and functional reverse remodeling. The mechanisms that facilitate the process of reverse remodeling have recently become the object of intensive research.

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Sympathetic innervation has been inversely correlated with cardiac function with patients with chronic HF (7,8). A reduced myocardial accumulation of iodine 123-*meta*-iodobenzylguanidine (^{123}I-*m*IBG) has been correlated with myocardial norepinephrine concentrations (9), myocardial cell injury (10), and adverse prognosis of patients with HF (7). However, little is known about sympathetic innervation during long-term unloading with an LVAD (11).

This study examined the effects of LVAD-induced unloading on cardiac function, structure, and hemodynamics and myocardial sympathetic innervation evaluated by ^{123}I-*m*IBG myocardial scintigraphy in patients with end-stage HF.

METHODS

Patient population. Consecutive HF patients who required LVAD implantation due to progressive deterioration because of their syndrome were included in the study. These patients were followed long term in our HF program, and the investigators were highly familiar with the natural history of their HF syndrome. Important baseline demographic, clinical, hemodynamic, and laboratory characteristics of each patient are shown in Table 1. All patients were in New York Heart Association HF functional class IV and refractory to optimal medical therapy. Four patients had diabetes (2 insulin dependent and 2 insulin nondependent). After LVAD implantation, all patients were treated with standard doses of a beta-adrenergic blocker, renin-angiotensin axis inhibitors, spironolactone, and digoxin. The LVADs used were HeartMate XVE in 2 patients, and HeartMate II (Thoratec Corporation, Pleasanton, California) in 10 patients. The HeartMate XVE was set to auto mode for optimal ventricular unloading, and the HeartMate II was fixed between 9,000 and 11,000 rpm, to reach a pulsatility index (estimated by the device's software) between 3 and 4.

At the time of enrollment in the study, the patients underwent echocardiography, Naughton protocol treadmill cardiopulmonary exercise stress testing to measure peak oxygen consumption, and right heart catheterization. These tests were repeated at 3 months after LVAD implantation when the patients had completely recovered from the surgical procedure and were fully active.

Patients with advanced chronic HF, LV systolic dysfunction, and an ejection fraction <30%, untreated with LVAD were also included in our study if they fulfilled the criterion of being optimally treated medically for ≥6 months. These patients were randomly chosen from the population followed in a long-term HF program. They underwent the same general evaluation (myocardial scintigraphy and functional and hemodynamic evaluations), were followed for a similar period of observations, and were treated with the same HF medications as the LVAD patients (standard doses of beta-adrenergic blockers, renin-angiotensin system inhibitors, spironolactone, and digoxin).

ABBREVIATIONS AND ACRONYMS

HF = heart failure
H/M = heart-to-mediastinum
LV = left ventricular
LVAD = left ventricular assist device
***m*IBG** = *meta*-iodobenzylguanidine

^{123}I-*m*IBG imaging. Baseline ^{123}I-*m*IBG imaging was performed in the fasting state, after withholding all medications on the morning of examination. Planar anterior images of the chest were obtained 1 h (early images) and 4 h (late images) after the intravenous injection of 111 to 148 MBq of ^{123}I-*m*IBG. All scans were acquired with a single-headed, tomographic Sophycamera DS7 digital gamma camera (Sopha Medical Vision International, Buc, France), with a 256 × 256 matrix on a dedicated Sophy NXT computer system (Sopha Medical Vision International) equipped with a low-energy, all-purpose, parallel-hole collimator using a 20% window centered on the 159-keV peak. Myocardial ^{123}I-*m*IBG activity was measured in a manually outlined region of interest surrounding the heart, excluding the ventricular blood pool, to standardize the cardiac uptake. A 20 × 15-pixel region of interest was also drawn over the upper mediastinum. The regions of interest were analyzed by a nuclear medicine expert unaware of the pa-

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Table 1. Individual Demographic, Clinical, and Laboratory Characteristics of the Study Sample

Patient #	Age/ Sex	Heart Failure		HR	LV		Pressures			CI	PVR	Vo_{2max}*	BNP	Na	Cr	Hgb	Furosemide
		Etiology	Duration (yrs)	(beats/min)	EF (%)	EDD (mm)	Systolic Brachial	Mean RA	Systolic PA	PCW	(l/min/m²)	(WU)	(ml/kg/min)	(pg/ml)	(mmol/l)	(mg%)	(g/dl)	(mg/day)
1	67/M	ICM	5	72	16	83	90	16	78	32	1.5	4.2	12.4	1,260	131	2.0	12.8	500
2	49/M	IDC	11	60	20	79	80	13	55	32	1.7	4.0	3.7	2,070	135	2.9	11.1	750
3	59/M	ICM	6	65	13	70	90	10	55	29	1.4	1.2	11.9	807	140	1.7	13.3	500
4	57/M	ICM	10	78	17	72	100	11	39	24	1.9	3.2	9.2	948	133	1.3	11.4	600
5	58/M	IDC	3	95	19	76	85	6	50	28	1.6	2.9	11.6	1,540	134	1.1	12.0	750
6	52/M	ICM	10	84	19	69	90	13	66	35	2.5	2.5	11.7	6,000	136	0.8	10.3	1,500
7	47/M	IDC	10	87	11	66	95	22	66	37	1.5	3.4	2.8	1,700	140	1.4	13.3	500
8	51/M	ICM	2	70	19	62	80	10	74	38	1.5	2.2	11.2	5,000	126	1.8	10.4	1,000
9	57/M	ICM	3	86	20	77	95	20	62	32	1.2	3.0	8.6	1,480	136	1.2	14.1	500
10	21/F	IDC	2	84	15	70	85	6	43	25	1.4	3.4	11.3	742	133	0.9	13.5	375
11	62/M	IDC	8	83	37	74	85	9	42	19	1.6	4.4	10.5	5,000	139	1.5	10.9	500
12	23/F	IDC	1	90	20	62	90	9	50	28	2.1	3.5	2.4	801	137	1.2	14.1	750

*If the patients were incapable of performing the exercise test immediately before LV assist device implantation, the most recent test performed within the past 2 months was used.
BNP = B-type natriuretic peptide; CI = cardiac index; Cr = creatinine; EDD = end-diastolic diameter; EF = ejection fraction; Hgb = hemoglobin; HR = heart rate; ICM = ischemic cardiomyopathy; IDC = idiopathic dilated cardiomyopathy; LV = left ventricular; Na = sodium; PA = pulmonary artery; PCW = pulmonary capillary wedge; PVR = pulmonary vascular resistance; RA = right atrial; Vo_{2max} = peak oxygen consumption; WU = Wood unit.

tients' clinical information. The heart/mediastinum (H/M) uptake ratio in early (H/M early) and late (H/M late) images was calculated, without background subtraction, as mean counts/pixel in the cardiac region of interest, divided by mean counts/pixel in the upper mediastinal region of interest.

Statistical analysis. The data are expressed as mean ± SD. The nonparametric Wilcoxon signed-rank test was used to assess the statistical significance of differences observed at consecutive time points. Correlations among the various variables were evaluated using Pearson's correlation coefficient. The nonparametric Spearman's correlation coefficient was used to assess associations of B-type natriuretic peptide changes with other parameters. The threshold of significance was set at $p = 0.05$. Statistical analysis was performed using the SPSS version 15.0 software (SPSS, Chicago, Illinois).

The study protocol was approved by our institutional review board, and after they had granted their informed consent, the patients were followed prospectively.

RESULTS

^{123}I-*m*IBG observations. After 3 months of LVAD support, H/M early increased from 1.35 ± 0.19 to 1.44 ± 0.11 ($p = 0.028$) and H/M late from 1.25 ± 0.18 to 1.43 ± 0.13 ($p = 0.01$) (Fig. 1). Furthermore, the washout rate significantly decreased from 51.0 ± 23.2% to 30.6 ± 8.7% ($p = 0.015$) (Fig. 2). In Figure 3, we show the observed improvement in H/M late in 1 of our patients (Patient #5 in Table 1). The abnormalities in baseline H/M early and washout rates in 6 patients with ischemic heart disease versus 6 patients with nonischemic heart disease were similar. However, after 3 months of LVAD support, the increase in H/M late among patients with nonischemic heart disease (0.23 ± 0.15) was more than twice that observed among patients with ischemic heart disease (0.10 ± 0.14), a difference that did not reach statistical significance, probably because of the small study sample.

Functional, structural, hemodynamic, and biochemical changes at 3 months. At 3 months of follow-up, echocardiographic, hemodynamic, functional, and biochemical changes were observed that were consistent with a significant improvement in clinical status (Table 2). A moderately strong correlation was found between the changes in H/M late and B-type natriuretic peptide ($R = 0.77$, $p = 0.01$) and systolic pulmonary artery pressure ($R = 0.7$, $p = 0.05$). Furthermore, a moderately strong correlation was

found between changes in systolic pulmonary artery pressure and H/M early and washout rate (R = 0.7, p = 0.04 for both correlations).

Observations in patients not treated with LVAD. In the 6 patients with HF who were not treated with an LVAD, a significant difference between baseline and 3 months was observed in neither the *m*IBG scintigraphic uptake nor their functional or hemodynamic status. However, the filling pressures tended to decrease between baseline and 3 months (Table 3).

DISCUSSION

In this study, LV unloading by an LVAD improved the sympathetic innervation of the failing heart assessed by ^{123}I-*m*IBG myocardial scintigraphy. Specifically, after 3 months of LVAD support, the H/M ratio on delayed images and the washout rate, the most important indicators of sympathetic innervation revealed by ^{123}I-*m*IBG imaging, were both significantly improved.

LVAD profoundly unloads the LV volumes and pressures, which reverses the compensatory and stress responses of the overloaded myocardium and might cause enough structural and functional reverse remodeling of the heart to allow a subset of patients to be weaned from the device after restoration of cardiac function (3–6). The mechanisms by which this reverse remodeling and eventually recovery occur are an area of active research, with the aim of identifying the factors associated with a sustained functional myocardial recovery (12). In several studies, mechanical unloading of the heart with an LVAD caused significant changes in a wide variety of biomarkers (13). Specifically, with regard to myocardial adrenergic innervation, long-term mechanical unloading restored the density of beta-adrenergic receptors in cardiomyocytes (14), normalized the distribution of the myocardial beta-adrenergic receptors (15), and enhanced the response to beta-adrenergic stimulation (16). A significant increase in the mRNA expression of the beta$_2$-adrenergic receptor has also been observed in the unloaded failing rat heart (17).

^{123}I-*m*IBG imaging is useful to grade the severity of HF and estimate its prognosis. Specifically, an accelerated washout rate and a decreased H/M ratio on delayed ^{123}I-*m*IBG images have both been correlated with LV dysfunction in patients presenting with HF, regardless of the underlying disease (7,8,18). Furthermore, the H/M ratio on delayed images and the washout rate have been widely recognized as reliable predictors of adverse cardiac events in patients with HF due to ischemic or nonischemic heart disease (7,19–24). Finally and importantly, comparative ^{123}I-*m*IBG scintigraphic studies obtained before and during treatment with renin-angiotensin axis inhibitors, beta-adrenergic blockers, or spironolactone showed an improvement in the washout rate and the H/M ratio on delayed images, associated with an improvement in cardiac function, indicating the contribution of this technique in the evaluation of therapeutic effects (8,25–28). This observation might have important implications, particularly for LVAD recipients whose native cardiac function is difficult to evaluate. Improvements in the ^{123}I-*m*IBG images could be used to identify responders to LVAD-induced unloading who might become candidates for explantation of the device after the development of a potentially sustained myocardial functional recovery.

To our knowledge this is the first study reporting improvement of myocardial sympathetic nervous ac-

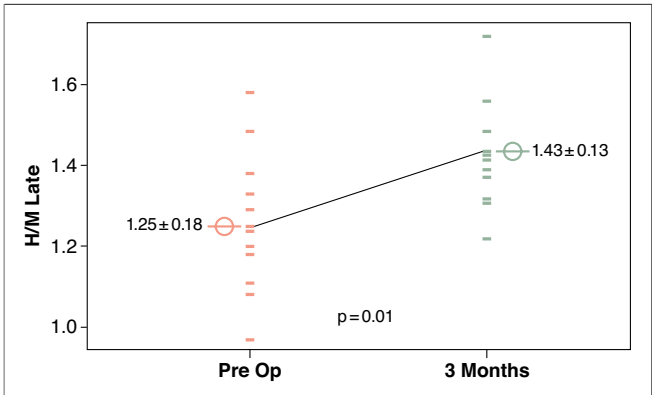

Figure 1. Effect of an LVAD on H/M Late Image

Changes in mean ± SD and individual heart-to-mediastinum (H/M) ratios in late images between baseline (Pre Op) and 3 months of left ventricular assist device (LVAD) support.

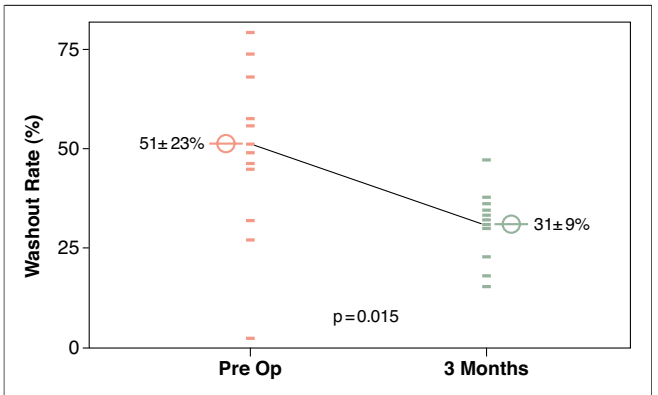

Figure 2. Effect of an LVAD on the Washout Ratio

Changes in mean ± SD and individual washout ratios between baseline (Pre Op) and 3 months of LVAD support. Abbreviations as in Figure 1.

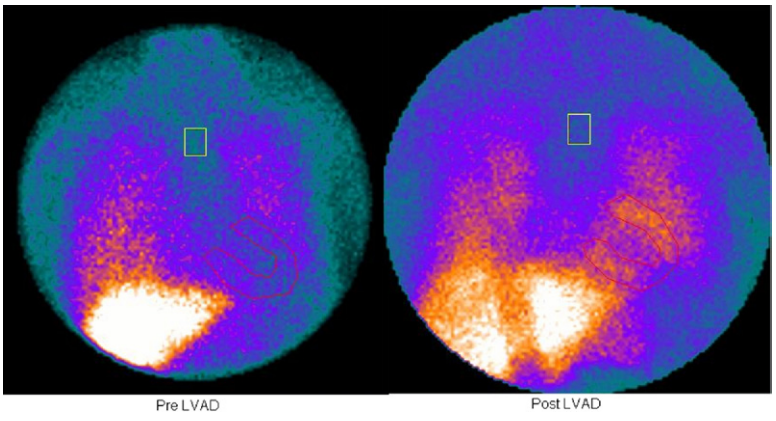

Figure 3. Effect of an LVAD on H/M Late Image

H/M uptake ratio in late image at baseline (Pre LVAD, zoom factor ×1) and after 3 months of LVAD support (Post LVAD, zoom factor ×1,2), Patient #5 in Table 1. Abbreviations as in Figure 1.

tivity during chronic mechanical unloading. Miyagawa et al. (11) observed no improvement in sympathetic nerve function, evaluated by ^{123}I-*m*IBG scintigraphy, after ≥2 months of LV support. However, the investigators noted that none of the 10 patients included in their study had evidence of cardiac functional or histological recovery during LVAD support, which they attributed to an incomplete mechanical unloading by left atrial drainage-type assist devices in the majority of patients. In contrast, in our study, the marked improvement in various functional, morphological, and biochemical characteristics observed after effective chronic mechanical unloading with the HeartMate XVE and II devices was accompanied by significant improvements in sympathetic innervation. The results of these 2 studies suggest that responders to LVAD-induced unloading can be identified by evaluating the functional recovery of the native heart with ^{123}I-*m*IBG imaging. The recovery of myocardial sympathetic innervation may be an important factor in the functional recovery of the myocardium during LVAD support, and ^{123}I-*m*IBG imaging might be used to evaluate the reverse remodeling that occurs during long-term mechanical unloading of the native heart. The correlation that we observed between scintigraphic improvements and changes in blood concentrations of B-type natriuretic peptide or changes in pulmonary artery pressures supports this hypothesis. The lowering of B-type natriuretic peptide blood concentrations is consistent with the suppression of adverse neurohormonal activation. Furthermore, increased filling pressures have been associated with adverse progression of remodeling (29–31).

Table 2. Baseline and 3-Month Clinical, Functional, Hemodynamic, and Biochemical Characteristics of the Study Sample

	Baseline	3 Months*	p Value
Heart rate (beats/min)	80 ± 11	66.7 ± 10.3	0.016
Systemic arterial blood pressure (mm Hg)			
Systolic	90 ± 8	89 ± 11	NS
Diastolic	62 ± 8	81 ± 10	0.005
Central blood pressures (mm Hg)			
Mean RA	12 ± 5	3.4 ± 1.8	0.012
Right ventricular systolic	57 ± 14	30 ± 7	0.028
Mean PA	38 ± 6	15 ± 5	0.018
PCW	30 ± 6	5 ± 3	0.012
CI (l/m^2/min)	1.7 ± 0.3	2.9 ± 0.8	0.012
PVR (WU)	3.2 ± 0.9	2.075 ± 1.0	0.041
LV			
EDD (mm)	72 ± 7	56 ± 3	0.002
EF (%)	19 ± 6	29 ± 9	0.006
Posterior wall end-diastolic thickness (mm)	8.2 ± 1.0	8.5 ± 0.9	0.196
Interventricular septum EDD (mm)	8.7 ± 1.1	8.8 ± 0.9	0.680
BNP (pg/ml)	1,510/877/3,535†	83/53/150†	0.003
Serum BUN (mg/dl)	76 ± 26	51 ± 23	0.028
Serum creatinine (mg%)	1.5 ± 0.6	1.0 ± 0.4	0.011

Values are mean ± SD unless indicated otherwise. *Echocardiographic, hemodynamic, and exercise capacity data were obtained with the LV assist device functioning at full support. †Values represent median/quartile 1/quartile 3, respectively.
BUN = blood urea nitrogen; NS = not significant; other abbreviations as in Table 1.

Study limitations. The limitations of this study include the small number of patients studied and the fact that the follow-up period was relatively short. Furthermore, the hemodynamic and echocardiographic data provided were obtained during full LVAD support and may not represent the native's heart functional performance during increased pressure and volume-loading conditions. Another limitation is the fact that the patients were not on exactly the same medical regimen before and after LVAD implantation. However, the included patients were on

the same classes of antiremodeling medications (beta-blockers and renin-angiotensin-aldosterone axis inhibitors) before and after LVAD therapy with the exception of 4 patients who were not administered beta-blockers and 2 patients who were not administered spironolactone in the pre-LVAD implantation period but received these agents post-implantation. In addition, in 1 of the included patients, no beta-blocker was administered, either before or after LVAD implantation, due to bradyarrhythmia. Noteworthy, however, in these particular patients, our ^{123}I-*m*IBG and functional findings were not different compared with the rest of the study patients.

CONCLUSIONS

LVAD-induced ventricular unloading caused clinical and hemodynamic improvements that were associated with improvements in the sympathetic innervation of failing hearts. Most importantly, the improvement in sympathetic innervation needs to be prospectively explored, with a view to identifying potential predictors of sustained functional myocardial recovery during or even before LVAD therapy.

Reprint requests and correspondence: Dr. John N. Nanas, 3rd Cardiology Department, University of Athens School of Medicine, 24 Makedonias, 10433 Athens, Greece. *E-mail: jnanas@ath.forthnet.gr*.

Table 3. Baseline and 3-Month Clinical, Functional, Hemodynamic, and ^{123}I-*m*IBG Scintigraphic Observations in 6 Patients Not Treated With LVAD

	Baseline	3 Months	p Value
H/M ratio in late images	1.29 ± 0.2	1.39 ± 0.2	NS
Washout rate (%)	51.1 ± 16.3	47.6 ± 20.5	NS
LV EDD (mm)	78 ± 20	77 ± 19	NS
LV EF (%)	22 ± 5	27 ± 8	NS
Heart rate (beats/min)	70 ± 9	70 ± 7	
Systemic arterial blood pressure (mm Hg)			
Systolic	104 ± 9	114 ± 13	NS
Diastolic	71 ± 0.4	73 ± 13	NS
Central blood pressures (mm Hg)			
Mean RA	9 ± 4	4 ± 2	NS
Right ventricular systolic	49 ± 10	33 ± 5	0.04
Mean PA	33 ± 9	21 ± 3	NS
PCW	22 ± 10	12 ± 6	
CI (l/m^2/min)	1.9 ± 0.3	1.9 ± 0.2	NS
PVR (WU)	2.0 ± 0.8	2.3 ± 1.1	NS
BNP (pg/ml)	850/745/1,179.5*	750/673.5/1,220*	NS
Serum BUN (mg/dl)	86 ± 54	92 ± 43	NS
Serum creatinine (mg%)	1.6 ± 0.6	1.6 ± 0.4	NS
Serum sodium (mmol/l)	138 ± 3	136 ± 2	NS
Hgb (g/dl)	13 ± 1.7	13 ± 0.8	NS
Daily furosemide dose (mg)	340 ± 173	410 ± 155	NS
NYHA functional class	II (67%)/III (33%)	II (67%)/III (33%)	NS
Peak Vo_{2MAX} (ml/kg/min)	17 ± 4	19 ± 5	NS

Values are mean ± SD. *Values represent median/quartile 1/quartile 3, respectively.
H/M = heart-to-mediastinum; NYHA = New York Heart Association; other abbreviations as in Tables 1 and 2.

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